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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US96/09603 <b>(22) International Filing Date:</b> 6 June 1996 (06.06.96) <b>(30) Priority Data:</b> 08/467,406 6 June 1995 (06.06.95) US <b>(71) Applicant:</b> NEUROBIOLOGICAL TECHNOLOGIES, INC. [US/US]; 1387 Marina Way South, Richmond, CA 94804 (US). <b>(72) Inventors:</b> JACOB, Peyton, III; 3787 Highland Road, Lafayette, CA 94549 (US). SHULGIN, Alexander, T.; 1483 Shulgin Road, Lafayette, CA 94549 (US). <b>(74) Agents:</b> SIEBERT, J., Suzanne et al.; Majestic, Parsons, Siebert & Hsue, Four Embarcadero Center, Suite 1450, San Francisco, CA 94111-4121 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>With amended claims.</i>
<b>(54) Title:</b> NOVEL N-SUBSTITUTED-2-AMINO-3',4'-METHYLENE-DIOXYPROPIOPHENONES  <b>(57) Abstract</b> <p>Novel compounds are provided having general formula (I), where R<sub>1</sub> is H, normal alkyl C<sub>1</sub> to C<sub>6</sub>, isopropyl, isobutyl, sec-butyl, t-butyl, allyl, propargyl, or cyclopropyl and salts thereof, and R<sub>2</sub> is H.</p> <div data-bbox="649 1197 1088 1344"><chem>CN(R1)(R2)C(C)C(=O)c1ccc2c(c1)OCO2</chem></div> <p style="text-align: right;">(I)</p>		

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NOVEL N-SUBSTITUTED-2-AMINO-3',4'-METHYLENE-  
DIOXYPROPIOPHENONES

Field of the Invention

The present invention generally relates to substituted aralkylamines, and more particularly to 2-alkylamino-3',4'-methylenedioxypropiofenones with biological activity such as central nervous system pharmacological activity.

Background of the Invention

Various drugs have been found useful to treat depression. Among these anti-depressant drugs are those that bind directly with some neurotransmitter receptors, particularly those which bind at serotonin uptake sites. Thus, the study of serotonin uptake sites is useful in the diagnosis and therapy of diseases, including depression. One means of making such measurements is by assays measuring competitive binding. For example, U.S. Patent 5,372,813, inventors Mathis, Jr. et al., issued December 13, 1994, describe competition assays with agonists and antagonists to the serotonin uptake system (from samples such as brain tissues) in measuring serotonin uptake sites.

Among commercially available prescription drugs is an anti-depressant call "Bupropion" (1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone), with preparations and pharmacology described in U.S. Patents 3,819,706 and 3,885,046. This anti-depressant is

known to be metabolized, in part, by reduction of the ketone group to the corresponding alcohol. Another commercially available prescription drug is Diethylpropion (1-phenyl-2-(N,N-diethylamino)-1-propanone) with preparation and pharmacology described in U.S. Patent 3,001,910.

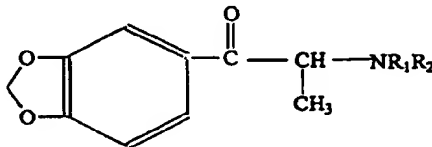
U.S. Patents 4,372,969, issued February 8, 1983, inventor Lafon, and U.S. Patent 4,508,732, issued April 2, 1985, inventors Hausberg et al. each describe compounds having an anti-depressant action on the central nervous system.

U.S. Patent 4,147,799, issued April 3, 1979, inventors Obase et al., describes 1-(3,4-methylenedioxyphenyl)-2-alkylaminoethanol compounds whose derivatives are said to show  $\beta$ -adrenergic receptor blocking activity.

Despite the known and presently available compounds, volume 29 of the *Annual Reports in Medicinal Chemistry* (1994) has noted the need for new anti-depressants, particularly a need for third generation anti-depressant agents that in addition to minimizing side-effects and toxicity in overdosage, would act in the first few days of treatment and would be effective in the vast majority of patients.

#### Summary of the Invention

Novel compounds are provided having the following general formula:

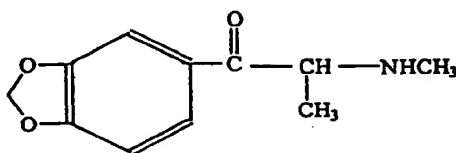


(Formula I)

3

where  $R_1$  is H, normal alkyl  $C_1$  to  $C_6$ , isopropyl, isobutyl, sec-butyl, t-butyl, allyl, propargyl, or cyclopropyl, and  $R_2$  is H.

A preferred embodiment is the compound where  $R_1$  is a methyl group and  $R_2$  is H:



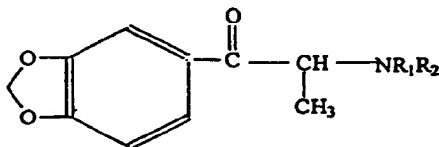
(Formula II)

The carbon atom of 2-methylamino-3',4'-methylenedioxypropiofenone that is beta to the carbonyl function is chiral, so that this target compound can exist in either of two optical forms, although the racemic mixture can be used.

Acute therapeutic levels of the Formula II embodiments are expected to be between about 100 and 150 mg for oral administration. The compounds have central nervous system activity, particularly anti-depressant and anti-Parkinson properties, and are also useful *in vitro* for diagnostic and assay applications, such as measuring serotonin or dopamine uptake sites.

#### Detailed Description of Preferred Embodiments

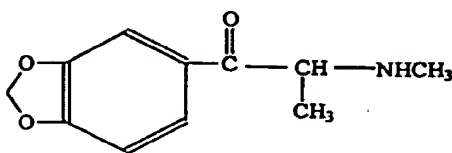
Novel compounds are provided having the following general formula:



(Formula I)

where R<sub>1</sub> is H, normal alkyl C<sub>1</sub> to C<sub>6</sub>, isopropyl, isobutyl, sec-butyl, t-butyl, allyl, propargyl, or cyclopropyl, and R<sub>2</sub> is H.

A preferred embodiment is the compound where R<sub>1</sub> is a methyl group and R<sub>2</sub> is H:



(Formula II)

We have coined the term "methyllone" for the Formula II embodiment.

Compounds of Formula I and their physiologically acceptable acid addition salts possess valuable pharmacological properties. Thus they exhibit, in particular, effects on the central nervous system, above all anti-depressant and anti-Parkinsonism activity. Illustrative of such activity are the following.

Compounds of Formula I bind to the serotonin uptake site. They also bind to the dopamine uptake site.

Compounds of Formula I and their physiologically acceptable acid addition salts can, therefore, be used as biologically active compounds and also as intermediate products for the preparation of other biologically active compounds.

Acid addition salts may be formed by reaction with either inorganic or organic acids. Thus it is possible to use inorganic acids, for example sulfuric acid, hydrogen halide acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as ortho-

phosphoric acid, nitric acid, or sulfamic acid, and also organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic, or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, such as  
5 formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic  
10 acid, nicotinic acid, isonicotinic acid, methanesulfonic acid, ethanesulfonic acid, ethandisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemonosulfonic acid, naphthalenedisulfonic acid, and laurylsulfuric acid.

15 ) Thus, the invention further relates to the use of the compounds of Formula I and their physiologically acceptable salts for the preparation of pharmaceutical formulations. In this connection they can be brought into a suitable dosage form together with at least one  
20 excipient or adjuvant and, if appropriate, in combination with one or more other active compound(s).

A variety of physiologic functions have been shown to be subject to influence by brain serotonergic neural systems. Generally, an "agonist" is a chemical  
25 compound that mimics the action of the endogenous neurotransmitter at receptors. Thus, serotonin agonists are chemical substances that bind to and mimic the action of serotonin on serotonin receptors (when direct-acting). Among uses for serotonin receptor agonists are as research  
30 and diagnostic tools. The inventive compounds can be used to measure serotonin and dopamine uptake sites in a sample, for example, by radiolabelling as is known to the art.

As earlier noted, the formulations can further include excipients, particularly when formulating for pharmaceutical uses. Suitable excipients are organic or inorganic substances which are suitable for enteral (for  
5 example oral) or parenteral administration or for local application, and which do not react with the new compounds, for example water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatins, carbohydrates, such as lactose or starch, magnesium stearate, talc or  
10 petroleum jelly.

Tablets, dragees, capsules, syrups, elixirs, drops or suppositories are especially used for enteral administration; solutions, preferably oily or aqueous solutions, and also suspensions, emulsions or implants are  
15 especially used for parenteral administration.

As compounds of this invention are water soluble salts, isotonic and sterile solutions can readily be made and used, for example, for the preparation of solutions suitable for injection. The formulations indicated can be  
20 sterilized and/or can contain adjuvants, such as lubricants, preservatives, stabilizing agents and/or wetting agents, emulsifiers, salts for regulating the osmotic pressure, buffer substances, colorants, flavoring substances and/or aroma generating substances. If  
25 desired, they can also contain one or more additional active compounds, for example one or more vitamins or mineral supplements.

The invention further relates to the use of the compounds of Formula I and their physiologically  
30 acceptable acid addition salts in combating diseases, particularly depressions of various etiologies and symptomatologies, and to their use in the therapeutic treatment of the human or animal body.



In this connection, the substances of this invention are generally administered in a manner analogous to that of known psychopharmacological agents which are commercially available (for example Imipramine), in dosages generally ranging from about 2-500 mg, particularly of 10-50 mg, per dosage unit. The daily dosage is preferably about 0.05 to 10 mg/kg of body weight. The particular dose for each specific patient depends, however, on a very wide variety of factors, for example on the activity of the particular compound employed, on the age, body weight, general state of health, sex, and diet of the patient, on the time and route of administration, on the excretion rate and combination of medicaments and on the severity of the particular disease to which the therapy applies. Oral administration is preferred.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Each of the compounds of Formula I mentioned in the examples which follow is particularly suitable for the preparation of pharmaceutical formulations.

The synthesis of the novel compounds is illustrated with three steps: (1) the synthesis of 3,4-methylenedioxypropiofenone; (2) the conversion of this intermediate ketone to the alpha-bromo derivative; and (3) the displacement of this bromo group with the appropriate amine to give the target compounds.

EXAMPLE 1AFirst Preparation of Intermediate Ketone 3,4-Methylene-dioxypropiofenone

To a well stirred solution of 10.6 g piperonal  
5 (0.1 mole) in 90 mL anhydrous ether under an argon  
atmosphere there was added, initially, 30 mL of a 2.0  
molar solution of ethyl magnesium chloride in anhydrous  
ether, at a rather rapid rate. There was the immediate  
formation of an intermediate of a cottage cheese  
10 consistency, with a modest increase of temperature. With  
external cooling, and additional 35 mL of the Grignard  
solution was added dropwise and the reaction mixture  
became thinner and more easily stirred. The reaction  
mixture was poured over 60 g cracked ice containing 3 mL  
15 concentrated sulfuric acid. The phases were separated,  
and the aqueous phase extracted with 2x50 mL methylene  
chloride. The organic phases were pooled, and stripped of  
solvent under vacuum. The remaining 13.03 g amber oil was  
distilled at 100-110°C at 0.3 mm/Hg to provide 11.37 g 1-  
20 (3,4-methylenedioxyphenyl)-1-propanol as a white oil. A  
repeat preparative run at a 1 mole level, yielded 88.4 g  
of the carbinol product. In both distillations, there was  
some evidence of decomposition at the distillation  
temperature and a GC-MS analysis of the pot residue showed  
25 the presence of two products, dimers, resulting from the  
cleavage of a molecule of water from one molecule of the  
product carbinol and an aromatic proton of a second  
molecule. A TLC analysis (silica gel, methylene  
chloride/hexane) showed the distilled product to be  
30 largely carbinol, with two impurities that had Rf's  
greater than that of the product.

A solution was made of 10 g potassium dichromate in 65 mL water containing 7 mL concentrated sulfuric acid. This was vigorously stirred, and cooled with an external water bath. A total of 11.7 g of 1-(3,4-methylenedioxyphenyl)-1-propanol was added without solvent, dropwise, over the course of 0.5 h, then heated on the steambath for an additional hour. The reaction mixture was poured into 2 L water, acidified with hydrochloric acid, and extracted with 3x100 mL methylene chloride. The pooled extracts were washed with dilute aqueous sodium bicarbonate, and the solvent was removed under vacuum, yielding 13.6 g of an amber oil. TLC analysis showed the material to be approximately 80% ketone, with the remaining fraction being starting carbinol. This crude product was recycled with another charge of dichromate (6.6 g potassium dichromate, 42 mL water and 4.5 mL concentrated sulfuric acid) as described above. Again there was an exothermic reaction taking place, with the generation of a dark color. After the addition was complete, the reaction mixture was heated on the steambath for 2.5 h, flooded with 1 L water, acidified with concentrated hydrochloric acid, and extracted with 3x75 mL methylene chloride. The pooled extracts were washed with aqueous sodium bicarbonate, and the solvent removed under vacuum. The residue, 6.32 g of crude product, was distilled at 135-145°C at 0.3 mm/Hg to yield 4.3 g of 3',4'-methylenedioxypropiofenone as a white oil. A repeat run employing 24.9 of twice distilled carbinol (still containing the two impurities with Rf's greater than the carbinol, provided 14.6 g of the ketone product, again as an oil. Infrared analysis showed the presence of both a carbonyl group and a hydroxy group, indicating the presence of unreacted carbinol. This was confirmed by GC-

MS, where the major product was the ketone (MW 178, major fragment 149) contaminated with unreacted carbinol (MW 180, major fragments 151, methylenedioxybenzyl; 121, methylenedioxyphenyl). Two minor impurities proved to be  
5 piperonal and trans-isosafrole, corresponding to the fast-moving TLC components.

#### EXAMPLE 1B

##### Second (and Preferred) Route to the Intermediate Ketone

A stirred mixture of 39 g methylenedioxybenzene,  
10 48 g propionic anhydride and 1.54 g elemental iodine was held at reflux temperature with a heating mantle for 3.5 h. The crude reaction mixture was freed of all volatiles that could be removed at 65°C, at the water pump, yielding 42 g of a heavy black oil. The distillate smelled  
15 strongly of propionic acid. (Attempts to purify or decolorize this thick crude product by acid, base, or bisulfite washing, were not successful.) The crude product was distilled at 0.1 mm/Hg. At 60°C a sizable quantity of clear colorless liquid distilled over (the  
20 temperature was maintained until the distillation was complete and the distillate was flamed into the traps). Between 100-125°C a pale brown fraction distilled over, weighing 28 g. This was dissolved in 200 mL methylene chloride and decolorized by washing with 2x600 mL water,  
25 each portion containing 1 g sodium bisulfite. Removal of the organic solvent under vacuum gave 27.1 g of a pale brown residue which was again distilled at 0.2 mm/Hg to give a fraction boiling at 90-115°C that was essentially white. This, on cooling, crystallized to give 3,4-  
30 methylenedioxypropiofenone as a mass of off-white solids, weighing 24.46 g. Analysis by GC-MS showed a single sharp

peak (about 97% purity) with a spectrum identical to the product from the Grignard reaction above. A reference sample without color was obtained by grinding a little of the distillate under a third its weight of cold methanol, followed by filtration. This sample had no detectable impurities by GC-MS.

#### EXAMPLE 2

##### Preparation of 2-bromo-3',4'-methylenedioxypropiofenone

A solution of 41.50 g 3,4-methylenedioxypropiofenone in 300 mL methylene chloride was treated with 94.2 g cupric bromide that had been powdered in a mortar, and held at reflux on a stem bath for 7 hours. TLC analysis showed it to be about two-thirds converted to the  $\alpha$ -bromo derivative (silica gel, methylene chloride as developing solvent, ketone  $R_f=0.7$ , bromoketone  $R_f=0.8$ ). An additional 94.2 g cupric bromide was added and the suspension held at reflux for an additional 6 hours. The reaction mixture was clarified by filtration and the inorganic solids washed with additional methylene chloride. The deep green combined filtrate and washings were filtered through a methylene chloride wetted bed of silica gel yielding a nearly colorless clear filtrate. This was stripped of solvent under vacuum, and the residue, 47.4 g, was distilled bulb-to-bulb. The product distilled at 100-140°C at 0.15 mm/Hg yielding 42.87 g of 2-bromo-3',4'-methylenedioxypropiofenone as a pale amber oil that set up to a crystalline solid. The GC-MS analysis showed the desired ketone as the major product (parent peaks, 256-258; major fragment 147, methylenedioxybenzoyl; 121, methylenedioxyphenyl, confirming the chain bromination of the propiofenone). A minor impurity

was 2-chloro-3',4'-methylenedioxypropio-  
phenone, seen with  
parent peaks at 212/214, and the major peaks again at 149  
and 121. It probably arose from the methylene chloride  
solvent, and does not interfere in any way with the  
5 subsequent aminative reaction.

### EXAMPLE 3

#### Preparation of 2-methylamino-3',4'-methylenedioxypropio- phenone

The last reaction needed for the synthesis of  
10 the target compound (the preferred "methylo-  
n-ment") is achieved by the displacement of the  $\alpha$ -bromo group  
with methylamine.

To a well-stirred solution of 10.8 g freshly  
distilled 2-bromo-3',4'-methylenedioxypropio-  
15 phenone in 70 mL sulfolane at room temperature there was added 23 mL of  
40% aqueous methylamine. There was a slight exothermic  
reaction (the temperature went up to 32°C) and after ten  
minutes the reaction mixture was quenched by pouring it  
into 2 L of water. This basic solution was extracted with  
20 4x100 mL of ether, and the pooled ether extracts back-  
extracted with 3x100 mL dilute sulfuric acid. These  
bright yellow extracts were made basic with saturated  
aqueous sodium carbonate, extracted with 3x100 mL  
methylene chloride which, after pooling and removal  
25 solvent under vacuum, yielded 4.11 g of a pale yellow oil.  
This was distilled at 0.1 mm/Hg to give a fraction boiling  
at 140-145°C that weighed 3.64 g. This was dissolved in  
30 mL of isopropanol, neutralized with about 50 drops of  
concentrated HCl, which produced a heavy crop of crystals.  
30 The mixture was diluted with an equal volume of diethyl  
ether yielding fine white crystals of 2-methylamino-3',4'-

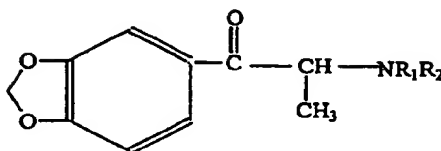
methylenedioxypropiophenone hydrochloride (methylone) which was removed by filtration, washed with ether, and air dried to constant weight (3.18 g, 32% yield). the infrared spectrum shows a carbonyl group at  $1680\text{ cm}^{-1}$ . The  
5 mass spectrum, as determined by GC-MS, showed an appropriate (but weak) parent peak at mass 207, and the major peak at mass 58 representing the nitrogen-containing fragment  $\text{C}_3\text{H}_8\text{N}^+$ . There is an accompanying peak (following, in the chromatographic separation) with a mass  
10 fragment 56,  $\text{C}_3\text{H}_6\text{N}^+$ , which is a characteristic artifact that generally accompanies the analysis of compounds with a  $\beta$ -aminophenone structure.

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It is to be understood that while the invention has been described above in conjunction with preferred  
15 specific embodiments, the description and examples are intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims.

It is Claimed:

1. A compound having the formula:

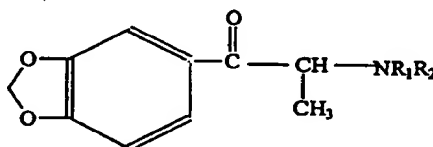


(Formula I)

where R<sub>1</sub> is H, normal alkyl C<sub>1</sub> to C<sub>6</sub>, isopropyl, isobutyl, sec-butyl, t-butyl, allyl, propargyl, or cyclopropyl and salts thereof, and R<sub>2</sub> is H.

2. The compound as in claim 1 wherein R<sub>1</sub> is a methyl group.

3. A pharmaceutical composition for alleviating depression of the central nervous system or alleviating symptoms of Parkinson's disease comprising:  
an anti-depressant or anti-Parkinsonism  
effective amount of a compound having the formula



(Formula I)

where R<sub>1</sub> is H, normal alkyl C<sub>1</sub> to C<sub>6</sub>, isopropyl, isobutyl, sec-butyl, t-butyl, allyl, propargyl, or cyclopropyl and salts thereof and R<sub>2</sub> is H; and,

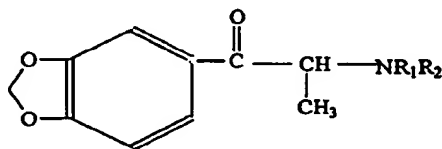
a pharmaceutically acceptable excipient.



4. A composition as in claim 3 wherein the Formula I compound is in a physiologically acceptable acid addition salt form.

5. A pharmaceutical composition as in claim 3 or 4 wherein  $R_1$  is a methyl group.

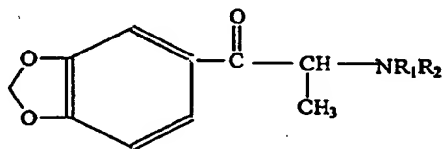
6. A ligand having binding activity for at least one serotonin or dopamine uptake site and having the formula



(Formula I)

5 where  $R_1$  is H, normal alkyl  $C_1$  to  $C_6$ , isopropyl, isobutyl, sec-butyl, t-butyl, allyl, propargyl, or cyclopropyl, and  $R_2$  is H.

7. A ligand having binding activity for at least one serotonin or dopamine uptake site and having the formula:



(Formula I)

5 where  $R_1$  is a methyl group and  $R_2$  is H.

## AMENDED CLAIMS

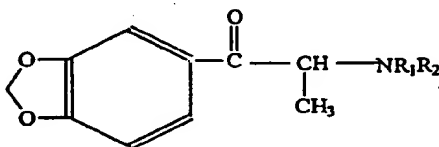
[received by the International Bureau on 14 August 1996 (14.08.96);  
original claims 3 and 7 amended; original claims 1, 2 and 6 cancelled;  
remaining claims unchanged (2 pages)]

1. CANCELLED

2. CANCELLED

3. A pharmaceutical composition for alleviating depression of the central nervous system or alleviating symptoms of Parkinson's disease in a human patient comprising:

5 an anti-depressant or anti-Parkinsonism effective amount of a compound having the formula



(Formula I)

where R<sub>1</sub> is H, normal alkyl C<sub>1</sub> to C<sub>6</sub>, isopropyl, isobutyl, sec-butyl, t-butyl, allyl, propargyl, or cyclopropyl and  
10 salts thereof and R<sub>2</sub> is H; and,  
a pharmaceutically acceptable excipient.

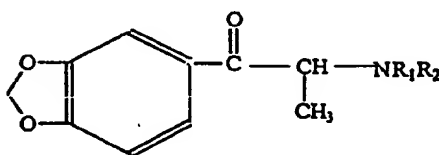
4. A composition as in claim 3 wherein the Formula I compound is in a physiologically acceptable acid addition salt form.

5. A pharmaceutical composition as in claim 3 or 4 wherein R<sub>1</sub> is a methyl group.

AMENDED SHEET (ARTICLE 19)

## 6. CANCELLED

7. A ligand having binding activity for at least one serotonin or dopamine uptake site and having the formula:



(Formula I)

- 5 where R<sub>1</sub> is H, normal alkyl C<sub>1</sub> to C<sub>6</sub>, isopropyl, isobutyl, sec-butyl, t-butyl, allyl, propargyl, or cyclopropyl, and R<sub>2</sub> is H.

AMENDED SHEET (ARTICLE 19)

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/09603

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/36; C07D 317/48

US CL : 514/466; 549/436

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/466; 549/436

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN CAS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chem. abstr., Vol. 54, No. 5, 10 March 1960 (Columbus, OH, USA), column 1, the abstract No. 4475i, SATODA, I. et al., 'Synthesis of $\beta$ -(2,5-dimethoxyphenyl)- $\beta$ -hydroxyisopropylamine.' Yakugaki Zasshi 1959, 79, 989-992, see entire abstract.	1, 3 and 4
X	US 3,523,954 A (H. KOPPE ET AL.) 11 August 1970 (11.08.70), column 1, lines 29-45.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

08 JULY 1996

Date of mailing of the international search report

24 JUL 1996

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